REMARKS

Claims 2-10, 27-31 and 33-37 are pending and under examination in the above-identified application. Applicants have reviewed the rejections set forth in the Office Action mailed November 19, 2004, and respectfully traverse all grounds for the reasons that follow.

Applicants would like to thank Examiners Strzelecka and Fredman for extending a telephonic interview with Applicant's representatives on April 19, 2005. The amendments above and remarks below are believed to substantially conform and be responsive to the subject matter discussed in the interview. In light of the interview and the remarks herein, Applicants' respectfully request that the Examiner reconsider and withdraw the pending grounds of rejection.

Rejections Under 35 U.S.C. § 103

Claims 2-10, 27-31 and 33-37 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Holmes, U.S. Patent No. 5,679,773, in view of Beattie, U.S. Patent No. 6,156,502. Holmes is alleged to describe a method of synthesis and release of nucleic acids, including cleaving oligonucleotide probes from a support to generate a pool of oligonucleotides. Beattie is alleged to teach a method of oligonucleotide fingerprinting (ASOF) where oligonucleotides cleaved from a solid support are contacted with a target nucleic acid. The Office concludes that it would have been obvious to one skilled in the art at the time of the invention to have used the assay of Beattie with the cleaved oligonucleotides from Holmes because Beattie describes that the ASOF assay can be used in several analyses without the need for electrophoresis. The Office further concludes that Applicants' previous response inappropriately argued the cited references individually and that the passage of Holmes "very strongly suggests creating pools of different oligonucleotide." Finally, the Office appears to admit that Beattie teaches away from the claimed invention, but that such teaching away "has no bearing on the combination of the two references."

The invention is directed to a method for multiplex detection of target nucleic acids. The method includes releasing first and second oligonucleotides from a substrate to generate a pool of first and second different oligonucleotides and contacting the released first and second different oligonucleotides with a composition having at least a first and second target nucleic

acid. Applicants respectfully submit that the cited combination of references fail to teach, suggest or provide a motivation to arrive at the invention as claimed.

Where an invention is contended to be obvious based upon a combination of elements across different references, the Federal Circuit case law "require that there be a suggestion, motivation or teaching to those skilled in the art for such a combination." *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 5 (Fed. Cir. December 14, 2004) (citing *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)). This requirement prevents the use of "the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." *Id.* (citing *Ecolochem, Inc. v. So. Cal. Edison Co.*, 227 F.3d 1361, 1371-72 (Fed. Cir. 2000) (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) (abrogated on other grounds)).

Regarding combinations of references

Taking in turn the Office's response to Applicants' previous response, Applicants respectfully point out that Applicants properly responded to the combination of cited references, rather than address the references individually. For example, Applicants stated:

> Initially, Applicants note that in contrast to the Examiner's characterization of the references, the combination of Beattie and Holmes does not teach or suggest all of the elements of the claims. That is, as noted above with respect to Beattie, there is no teaching in Holmes Beattie or the combination of the two of a method that includes cleaving linkers to arrive at a pool of oligonucleotides comprising said first and second different oligonucleotide" as claimed.

Response, p.10, last para. (emphasis added); *see also* Response at p.11, third para.

In light of these passages, Applicants' maintain that the combination of references was properly addressed and reassert these arguments of record.

Regarding a pool of oligonucleotides comprising first and second different oligonucleotides

The Office further contends that the "passage of Holmes cited by Applicants very strongly suggests creating pools of different oligonucleotides, since they do not specifically teach individually releasing single types of oligonucleotides." Office Action at page 3. The passage at issue states:

> [S]mall beads may be provided on the surface, and compounds synthesized thereon may be released upon completion of the synthesis.

Col. 6, lines 36-37.

Applicants maintain that there is nothing in this passage that teaches or suggests generating pools of different oligonucleotides. The Office appears to rely on the *lack* of a specific teaching for releasing single types of oligonucleotides as support for suggesting pools of different oligonucleotides. Applicants respectfully disagree. Silence does not constitute a teaching or suggestion for a claimed element if the element is not there. Moreover, failure to describe an element also cannot be characterized as a strong suggestion.

Regardless of certain descriptions in Holmes appearing to describe diverse populations of polymers, there is no showing of record or rationale described in Holmes for releasing a mixture of oligonucleotides from an array precisely assembled to have oligomers displayed at specific locations just to thereafter combine them into a pool of mixed oligonucleotide species. Furthermore, the context in which Holmes describes cleaving oligomers from a substrate is consistent with cleavage to form homogeneous species of oligomers and is inconsistent with cleavage to form a pool of oligonucleotides comprising first and second different oligonucleotides. For example, the passage at column 12, lines 6-16, cited by the Office, describes releasing oligomers for the purpose of characterization or for use in subsequent bioassays. Holmes also describes cleavage of labeled polymers and comparison with known standards to confirm synthesis fidelity (see column 19, lines 49-52). One skilled in the art would have understood that oligomers released in accordance with the methods of Holmes would have been characterized or assayed as individual species in accordance with standard analytical methods at the time of filing. Nowhere does Holmes, taken alone or in combination with Beattie, teach or suggest a method that can be used to confirm synthesis fidelity for a released pool of oligonucleotides comprising first and second different oligonucleotides. Similarly, the cited references do not teach or suggest a characterization method or bioassay that would be useful for a released pool of oligonucleotides comprising first and second different oligonucleotides.

Absent a teaching or suggestion of all claimed elements, including, for example, generating a pool of oligonucleotides comprising first and second different oligonucleotides, the Office has not satisfied its burden of establishing a *prima facie* case of obviousness. *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974); M.P.E.P. §2143.03 (establishing a *prima facie* case of obviousness requires that all the claim limitations must be taught or suggested by the prior art).

Regarding teaching away

The absence of teaching or suggestion of all of the claimed elements, as set forth above, is sufficient to overcome the obviousness rejection. Nevertheless, Applicants further maintain that the combination of references is improper because the cited art teaches away from the claimed invention.

The Office appears to erroneously dismisses the teaching away in the cited art. Applicants pointed out in their previous response that Beattie teaches away from the generation of a pool of different oligonucleotides. For example, Applicants stated:

> [I]f the synthetic reactions were "mixed" or "pooled", the result would be that there would be a mixture of different oligonucleotide sequences at any particular spot on the array. Beattie clearly teaches that this is not the case. . . . In teaching that all embodiments of the ASOF technique require that each sequence is located at a specific site, Beattie clearly demonstrates that any pools of oligonucleotides do not include first and second different nucleotides. Accordingly, Beattie fails to teach a method that includes generation of a pool of oligonucleotides comprising said first and second different oligonucleotides as claimed.

Response, p.9, first paragraph.

The Office acknowledges "the fact that Beattie teaches away from having different pools of oligonucleotides" but goes on to allege that this "has no bearing on the combination of the two references since Beattie is relied upon for the limitation of contacting cleaved oligonucleotides with target nucleic acids, which Holmes teaches implicitly by teaching sequencing by hybridization and using oligonucleotides in bioassays."

First, Applicants respectfully point out that the Office's apparent conclusion is contrary to Federal Circuit precedent. A long line of Federal case law has established that obviousness can be rebutted where it is shown that the prior art taught away from the claimed invention. *Iron*

Grip Barbell, Case No. 04-1149, slip op. at 7, *citing In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997). A teaching away can be established where the cited art discourages the solution of the claimed invention. *In re Fulton*, Case No. 04-1267, slip op. at 8 (Fed. Cir. December 2, 2004). The cited references must be considered in their entirety. Thus, dismissal of the teaching away present in a cited reference merely because the references is relied upon for a particular element, is improper.

Second , the element of the claim for which Beattie is relied upon by the Office is germane to the alleged motivation. Specifically, the Office asserts that "Beattie is relied upon for the limitation of contacting cleaved oligonucleotides with target nucleic acids." A relevant issue is whether the cleaved oligonucleotides are homogeneous, having only a single species, or whether they are a pool of oligonucleotides comprising first and second different oligonucleotides, as claimed.

As pointed out in the previous response, the passages in Beattie relied upon by the Office in regard to the "the limitation of contacting cleaved oligonucleotides with target nucleic acids" (specifically, Col. 8, lines 30-39 and Col. 12, lines 57-64) refer to methods for synthesizing oligonucleotides for use in producing a spotted array. See page 8, line 20 through page 9, line 20 of the response mailed April 22, 2004. The methods described by Beattie are clearly directed to release of homogeneous populations of oligonucleotides because if the synthetic reactions were "pooled", then this would result in a mixture of different oligonucleotide sequences present at any particular spot on the array. Beattie clearly teaches that this is not the case in asserting that:

> A *key* feature, common to <u>*all* embodiments</u> of the arbitrary sequence oligonucleotide fingerprinting technique of the present invention, is the use of a set of arbitrary sequence oligonucleotide probes, *each sequence located at a specific site* on a hybridization support via binding of the short strands to the surface at one end.

Col. 4, lns. 5-10 (emphasis added).

The language used by Beattie clearly establishes that the release of oligonucleotides in his methods produces homogeneous oligonucleotide solutions, not merely as one alternative, but as the only method for satisfying <u>all embodiments</u> of the arbitrary sequence oligonucleotide

fingerprinting technique to which the patent is directed. Thus, Beattie teaches away from the alleged combination of references.

Regarding lack of motivation to combine the cited references

The absence of teaching or suggestion of all of the claimed elements or, independently, the teaching away by the cited references, as set forth above, is sufficient to overcome the obviousness rejection. Nevertheless, Applicants further submit that there would not have been motivation to combine the references to arrive at the claimed invention.

Even assuming *arguendo* that Holmes in some way suggested creating a pool of oligos, the alleged combination of using the assay of Beattie with the cleaved oligonucleotides from Holmes would have been inoperable. As described in the passages cited by the Office, Beattie describes making arrays using the spotting technique. For example, at column 8, lines 30-48, Beattie describes an improved method of preparing oligonucleotide arrays in which *inter alia* oligonucleotides are synthesized on controlled pore glass supports, cleaved and applied to a glass or silicon dioxide surface such that covalent bonds are formed between the oligonucleotides and surface. A similar spotting technique is described in the paragraph spanning columns 12 and 13. The use of a pool of oligonucleotides, whether or not produced by the methods of Holmes, for spotting on the arrays of Beattie would result in spots each containing mixtures of oligonucleotides. However, as pointed out previously Beattie teaches that "A key feature, common to *all* embodiments of the arbitrary sequence oligonucleotide fingerprinting [ASOF] technique of the present invention, is the use of a set of arbitrary sequence oligonucleotide probes, *each sequence located at a specific site* on a hybridization support via binding of the short strands to the surface at one end." Emphasis added, column 4, lines 5-10. Thus, an array produced in accordance with the alleged combination would not be operable in any of the embodiments of the ASOF techniques of Beattie.

Moreover, under the section entitled "Rationale of ASOF" (see Example I), Beattie teaches that the fingerprinting experiments are carried out to identify specific oligonucleotides that are capable of revealing polymorphisms (see column 14, lines 4-10). However, if each spot contained a mixture of oligonucleotides, it would not have been possible to identify a *single* oligonucleotide that reveals a polymorphism in the methods of Beattie. Thus, the combination of

references would not work for the purposes described by Beattie. Accordingly one skilled in the art would not have been motivated to make the alleged combination to arrive at the claimed invention.

In light of the remarks above, Applicants maintain that the claimed invention is unobvious over Holmes in view of Beattie because the cited combination fails to teach, suggest or provide any motivation to arrive at the invention as claimed. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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